REMARKS

Because the application is under Final Rejection, Applicant files a Response by December 16, 2008 in order to obligate the Examiner to issue an Advisory Action. Claims 7, 9, 28 and 29 are pending, and all of the pending claims are rejected. Applicant appreciates the success in overcoming the prior art rejections under 35 U.S.C. 102(b) in the last Response.

Rejection under 35 U.S.C. 112, first paragraph

The Examiner's Position

The Examiner rejects claims 7, 9, 28 and 29 as not properly enabled even in view of the arguments Applicant presented in the Response filed June 27, 2008. The Examiner says that this data does not support treating ovarian cancer since it is unclear how the mouse model of melanoma relates to treating ovarian cancer (e.g. different cell types, different etiologies, different treatments, and different CDCP1 expression). In short, the Examiner says that the data Applicant presented is not from an art accepted animal model for ovarian cancer. Further, regarding claim 28, it is allegedly unclear whether an antibody fragment would work at all. The Examiner refers to many properties of an antibody such as ADCC and CDC that an antibody fragment does not possess. Further, antibody fragments include Fab' fragments that would allegedly not crosslink CDCP1 receptors on the surface of cells.

Applicant's Position

The Examiner states that the specification does not disclose any *in vivo* data on the ability of the antibody to bind CDCP1 to treat ovarian cancer. However, as acknowledged by the Examiner in the Office Action, *in vivo* data is not required by the United States patent law in order to fulfill the enablement requirement. Nevertheless, as explained in further detail below, Applicant has submitted both *in vitro* and *in vivo* data clearly demonstrating that an anti-CDCP1 antibody is an effective ovarian cancer therapy.

1. *Applicant provides data demonstrating that an antibody-dependent cellular cytotoxicity (ADCC) assay was performed on the human ovarian tumor cell line SKOV-3 in the presence of the CDCP1-specific antibody (Ab 002-G07).*

The Declaration under 37 C.F.R. 1.132 of Sean Mason, Ph.D. submitted on November 20, 2007 provides data demonstrating that an antibody-dependent cellular cytotoxicity (ADCC) assay was performed on the human ovarian tumor cell line SKOV-3 in the presence of the CDCP1-specific antibody (Ab 002-G07). As explained in the Declaration on pages 2 and 3 and shown in Figure 1, the ADCC assays reveal that the human ovarian tumor cell line SKOV-3 was lysed in the presence of Ab 002-G07 in an antibody dose-dependent manner. The ADCC assay shows that the anti-CDCP1 antibody recruits the effector cells to lyse the ovarian cancer cells expressing CDCP1 on the cell surface. Accordingly, this data demonstrates that an anti-CDCP1 antibody has cell lysis activity on an ovarian cancer cell line and, therefore, may be used as an effective method for treating ovarian cancer. In this regard, Applicant respectfully submits that data has already been provided to the Examiner that unequivocally demonstrates that the present claims meet the enablement requirement.

2. *Applicant now submits further data of an antibody-dependent cellular cytoxicity (ADCC) assay performed on a different human ovarian cancer cell line OVCAR-3 using the anti-CDCP1 antibody Ab 002-G07 previously tested on SKOV-3 cells.*

In addition to the above data provided in the Declaration of Sean Mason, Applicant now submits further data of an antibody-dependent cellular cytoxicity (ADCC) assay performed on a different human ovarian cancer cell line OVCAR-3 using the anti-CDCP1 antibody Ab 002-G07 previously tested on SKOV-3 cells. Figure 4 submitted herewith demonstrates that the antibody shows a dose-dependent effect on OVCAR-3 cell lysis. The percent lysis of the OVCAR-3 cells differs from the values previously presented for SKOV-3 due to variations caused by different donor effector cells and cell labeling. Applicant submits that such variations are expected in the art, and the values of percent specific lysis for the OVCAR-3 cells are sufficient to demonstrate that the antibody is causing ADCC lysis in a dose-dependent manner. Accordingly, this data is further evidence that an anti-CDCP1 antibody has cell lysis activity on ovarian cancer cell lines and, therefore, may be used as an effective method for treating ovarian cancer.

3. *Further in vivo data is not required in order to meet the enablement requirement of 35 U.S.C. 112, first paragraph.*

Applicant submits that further *in vivo* data is not required in order to meet the enablement requirement of 35 U.S.C. 112, first paragraph. One of ordinary skill in the art clearly understands that *in vitro* assay data demonstrating cytoxic activity of an antibody directed to an

antigen expressed in cancer cells is sufficient evidence that the antibody may be used as a therapeutic agent for treating cancer *in vivo*. In support of this, many antibody therapeutics currently on the market were developed on the basis of *in vitro* studies. Clynes *et al., J. Nat Med.* 2000; 6(4): 443-446 (reference submitted previously with the Declaration of Sean Mason submitted November 20, 2007) teach on page 443, right column that therapeutic developed antibodies against the HER2/neu growth factor receptor prevent the growth of breast carcinoma cells and antibodies against the CD20 antigen on B cells arrest the growth of non-Hodgkin's lymphoma that were developed based on their ability to interfere with tumor cell growth *in vitro*. Therefore, Applicant submits that the *in vitro* assay studies on human ovarian cancer SKOV-3 cells is sufficient to show that an anti-CDCP1 antibody may be used to treat ovarian cancer.

4. Applicant provides in vivo data using a mouse model of ovarian cancer.

In addition to the above *in vitro* data for ovarian cancer cell line SKOV-3, Applicant has also provided *in vivo* data using a mouse model of ovarian cancer. As set forth in the Declaration under 37 C.F.R. 1.132 of Sean Mason, Ph.D. submitted on November 20, 2007, B16 F10 murine melanoma cells were used to develop an ovarian cancer model by expression of CDCP1 on the cell surface. The Declarant also describes how B16 F10 cells have been successfully used as a cancer model by transfecting and expressing the antigen EpCAM in the B16 F10 cells (*citing*, Lutterbuese *et al., Cancer Immunol Immunother.* 2007; 56(4), 459-468). In the present study of an anti-CDCP1 antibody, B16 F10 cells were transfected to express CDCP1, thereby providing a suitable mouse model of human ovarian cancer.

5. The levels of CDCP1 expressed by the B16F10-Luc Clone O cells are sufficiently similar to the human ovarian cancer cells to show that the mouse B16F10-Luc model was a suitable in vivo model of ovarian cancer for testing ovarian cancer therapies.

The Examiner says that transfected B16 F10 cells is not a suitable ovarian cancer model because the concentration of CDCP1 expressed in the mouse cells may be significantly higher than on ovarian cancer cells. In response, Applicant submits herewith Figures 5 and 6 showing the results of flow cytometry analyses. In Figures 5a and 5b the human ovarian cancer cell lines SKOV-3 and OVCAR-3 were labeled with the anti-CDCP1 antibody Ab 002-G07 (white peaks) or FITC-specific isotype control (shaded peaks). Figures 6a and 6b show the results for SKOV-3

cells and B16 F10-Luc Clone O cells using a different anti-CDCP1 antibody Ab 004-D03 that was derived from the same phage library as Ab 002-G07 and comprises human variable region sequences fused to human IgG1 constant domains. Figures 5 and 6 demonstrate that the human ovarian cancer cell lines have a range of CDCP1 expression levels. The expression profile for the B16F10-Luc Clone O in Figure 6b was shown to be substantially the same as the human ovarian cancer cell lines. The slightly wider range of expression for the B16F10-Luc Clone O cells compared to SKOV-3 and OVCAR-3 which was expected for a recombinant cell line. Nevertheless, Applicant submits that the levels of CDCP1 expressed by the B16F10-Luc Clone O cells are sufficiently similar to the human ovarian cancer cells to show that the mouse B16F10-Luc model was a suitable *in vivo* model of ovarian cancer for testing ovarian cancer therapies. Applicant also submits that, in any case, one of ordinary skill in the art knows that the degree of cell lysis does not necessarily correlate with the level of target antigen expression.

6. *The results from mouse in vivo studies may be used to demonstrate the effectiveness of the anti-CDCP1 for human in vivo studies.*

The results of *in vivo* studies performed using the CDCP1 transfected B16 F10 cells are shown in Figure 3a and demonstrate a dramatic reduction in tumor growth in mice treatment with the anti-CDCP1 antibody compared to the control treatments. As discussed above, the results from mouse *in vivo* studies may be used to demonstrate the effectiveness of the anti-CDCP1 for human *in vivo* studies. Therefore, Applicant submits that the *in vivo* study in mice provides further evidence that the anti-CDCP1 antibody may be used as a therapeutic to treat ovarian cancer.

7. *It is well known in the art that antibody fragments may be used as therapeutics.*

With respect to the use of antibody fragments, the Examiner states that there are many properties of a full length antibody such as ADCC and CDC that an antibody fragment would not possess. While certain antibody fragments may not possess the full effector recruitment activities of a full length antibody, Applicant submits that this does not mean that antibody fragments targeted to CDCP1 may not be used for therapy. It is well known in the art that antibody fragments that interact with a target antigen may be conjugated to cytotoxic moiety such as a drug moiety, a radionuclide, a protein such as a further whole or fragment of an antibody or an effector molecule. Such conjugates are discussed in detail in the description of

the present application on pages 2 to 5. Furthermore, antibody fragments may exhibit cytotoxic effects without the need for the full constant region of the full length antibody. Clynes *et al., J. Nat Med.*2000 6(4): 443-446 (submitted together with the Response on November 20, 2007) teach on page 445 the 225 that the antibody against epidermal growth factor receptor was able to reduce the epithelial tumor cell A431 *in vivo* as an $F(ab')_2$. Therefore, even if an antibody fragment does not possess the full ADCC or CDC activity of the full length antibody, it may still be used for therapies.

8. Antibody technology is relatively predictable.

Applicant submits that the teachings of the present specification meet the requirement of 35 U.S.C. § 112 as regards method of treatment claims. In particular, it has never been the law that clinical data must be available to meet the enablement requirement of 35 U.S.C. § 112. Applicant respectfully reminds the Examiner that in *Glaxo v. Teva* (2004 WL 1875017 D. Del 2004), the court concluded that there is no requirement in the law for working examples. Thus the fact that there is no clinical data in the specification does not render a rejection under 35 U.S.C. §112 proper.

Methods for making, screening and administering antibodies were routine in the art at the time the instant application was filed, and the association between the specific diseases is taught in the instant specification as filed. Yet, the Examiner maintains the rejection that the present specification does not teach how to make and use the invention as claimed. While the development of novel cancer therapeutics may in some instances be unpredictable, antibodies are distinguishable from simple new chemical entities (i.e. compounds which are simply inhibitors). This distinction can be drawn in part due to the high specificity of antibodies to the target protein and the functional interrelation of an antibody and a target protein. In support of this fact, Applicant submits two articles herewith, discussing the success rate of antibody pharmaceutical products, Ziegelbauer *et al., Journal of Commercial Biotechnology* 14(1):65-72 (2008) and Reichert *et al., Drug Discovery* 3:383 (2004). In particular Zeigelbauer *et al.* teach as follows:

> "Therapeutic antibodies have a high drug approval success rate once they reach clinical testing (29 percent for chimeric antibodies, 25 per cent for humanized antibodies compared to a success rate of approximately 11 per cent for small molecules).[7] In addition, much of the development and clinical experience that is gained from the generation and optimization of one antibody product can be readily applied to subsequent therapeutic antibodies,

diminishing some of the development, manufacturing, and clinical risks that are intrinsic to drug development.

Owing to their exquisite specificity and ability to affect unique biological functions, monoclonal antibodies have the potential to provide a continued source of effective, safe, and reliable therapies. The introduction of such new therapies will benefit patients having a variety of debilitating diseases that otherwise respond poorly to alternate approaches. Based on the impact of the successful discovery of novel antibody functions on the current portfolio of antibody drugs, it is likely that the ability to continue to engineer novel functionalities by using new antibody formats will drive the expansion of the antibody drug market in the future."

Applicant submits that biological type products are much more likely (perhaps 4 or 5 times more likely) to be commercialized than a new chemical entity. Applicant submits that this in part is due to the specificity of antibodies in a biological context. Thus, relatively speaking, Applicant submits that the unpredictability in the field under consideration is lower (perhaps significantly lower) than in other therapeutic fields.

9. *The USPTO guidelines for determining whether a specification is enabling for the claimed invention recognize that the specific facts and the state of the art must be considered in each instance such that no absolute rule exists.*

Applicant respectfully directs the Examiner to USPTO educational materials provided in a presentation by Jean Witz http://www.cabic.com/bcp/031208/JWitz_ECTT.ppt, a copy of which is enclosed. The USPTO educational materials indicate that:

- That the amount of guidance or direction required to enable an invention is inversely proportional to the amount of knowledge in the art (one of ordinary skill in the biotech field is highly skilled);
- All the evidence must be weighed up by the Examiner;
- There are no rules *per se* (i.e., that apply unilaterally across the board); and
- The analysis should be performed on a case-by-case basis.

Applicant further reminds the Examiner that the Examiner has the initial burden to establish a reasonable basis to question the enablement provided, that there must be a reason to doubt the objective truth of the statements contained in the specification, that references should be supplied if possible to support a *prima facie* case of lack of enablement, and that specific technical reasons (to support a *prima facie* case of lack of enablement) are always required. Applicant respectfully submits that the Examiner has failed to establish such a reasonable basis to question

the enablement provided. Further, the Examiner has not established specific technical reasons to support the allegation that the specification does not enable the methods of treatment claimed. Still further, the Examiner has provided no references supporting such an allegation.

Applicant further submits the following points:

- The present claims are not directed to a **cure** for the particular cancers but are directed to a method of treating certain cancers. Even established treatments including chemotherapy and radiotherapy are not successful in one hundred percent of cases but are still valid methods of treatment.
- The claimed treatment may ultimately need to be used in combination with other treatments in a cocktail (this does not reduce the value of the present treatment as a component of the cocktail).
- Whether certain products make it to the market is sometimes a commercial decision based on a number of factors including the timing to the market and resources to support projects and therefore products that make it to market is not a good indication of unpredictability in the art.

Respectfully, Applicant submits that one of ordinary skill in the art could make and use a "method of treatment..." according to the present claims without undue experimentation. Hence, a rejection under 35 U.S.C. §112, first paragraph as regards enablement is improper.

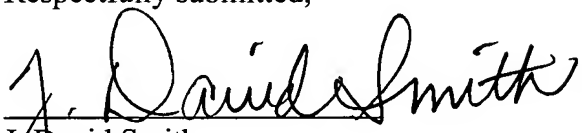
Fees

No fees are believed to be necessary in conjunction with this Response. However, should this be in error, authorization is hereby given to charge Deposit Account No. 11-1153 for any underpayment or to credit any overpayment.

Conclusion

It is submitted that the claims are in condition for allowance. In the event that there are any issues that can be resolved by way of telephone, the Examiner is invited to telephone the undersigned at the number indicated below.

Respectfully submitted,



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Date: December 12, 2008

Enclosures